C1 Esterase Inhibitor (RUCONEST®)
National Drug Monograph
June 2015
VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information[1,2]

Description/Mechanism of Action	C1 esterase inhibitor (RUCONEST) is a recombinant analogue of human complement component 1 esterase inhibitor for intravenous injection and is purified from the milk of transgenic rabbits.[1] It is also referred to as rhC1INH in the literature (for recombinant human C1 esterase inhibitor). C1 esterase inhibitor (C1INH) is found in human blood and is a serine protease inhibitor that is involved in the regulation of the complement and intrinsic coagulation or contact system pathway, as well as the fibrinolytic system. C1 inhibitor forms a complex with the protease causing inactivation. When there are low levels of functional C1INH, activation of the above pathways is not regulated. Treatment with C1INH results in an increase in plasma levels of C1INH to help regulate activation of the contact system, by inactivation of coagulation factor XIIa and kallikrein, preventing the release of bradykinin, which is thought to be responsible for the symptoms associated with hereditary angioedema (HAE) and increased vascular permeability.[2]
Indication(s) Under Review in this document	C1 esterase inhibitor [recombinant] (RUCONEST) is indicated for the treatment of acute attacks in adult and adolescent patients with hereditary angioedema. Limitation of Use: Effectiveness was not established in HAE patients with laryngeal attacks.
Dosage Form(s) Under Review	C1 esterase inhibitor [recombinant] (RUCONEST) is available as a lyophilized powder for reconstitution for injection in a single-use 25 mL glass vial. Each vial contains 2100 IU of rhC1INH.
REMS	☐ REMS ☒ No REMS ☐ Post-marketing requirements
Pregnancy Rating	Category B

Executive Summary

Efficacy[1,3-5]	• In one trial evaluating patients presenting with an acute HAE attack within 5 hours of onset, the primary efficacy endpoint of time to onset of sustained relief was significantly shorter in patients treated with rhC1INH compared to placebo (90 minutes vs. 152 minutes; P=0.031). The secondary endpoint of time to minimal symptoms was also shorter with rhC1INH at 303 minutes, but was not statistically significant compared to placebo at 483 minutes. • The open-label extension phase of this trial reported similar response with treatment of rhC1INH for repeated attacks.
Safety[1]	• Contraindications include: known or suspected allergy to rabbits and rabbit-derived products; history of immediate hypersensitivity reactions, including anaphylaxis, to C1 esterase inhibitor preparations. • Hypersensitivity reactions, including anaphylaxis may occur; if symptoms occur, discontinue rhC1INH and administer appropriate treatment. • Serious arterial and venous thromboembolic events have been reported at the recommended dose of plasma derived C1 esterase inhibitors (pdC1INH) in patients with risk factors. It is recommended to monitor patients with known risk factors for thromboembolic events during and after rhC1INH administration. • The most common adverse reactions reported in clinical trials with rhC1INH include headache, nausea and diarrhea.

Other Considerations[1,6,7]	- Three C1INH products are available: two are derived from human plasma (pdC1INH), and have the potential for human viral transmission (both pdC1INH products undergo several steps in the manufacturing process to reduce the risk of viral transmission, with neither product confirmed to be associated with a viral transmission); rhC1INH is purified from the milk of transgenic rabbits to reduce the risk for human viral transmission. - The available C1INH products differ in their FDA approved indications. There are no direct comparison trials to determine if there is a difference in efficacy or safety. - Per the manufacturer's product information, results of a planned subgroup analyses did not demonstrate a significant difference between treatment and placebo in the primary efficacy endpoint in the U.S. patients (98 minutes with rhC1INH vs. 90 minutes with placebo; whereas, there was a significant response in non-U.S. patients. There was also a larger treatment effect in the subgroup of men compared to the response in women. The product information states a potential explanation for the regional difference in response may be due to the large placebo response in U.S. women.
Potential Impact[1-16]	Projected place in therapy: overall, rhC1INH appears to be effective in reducing the time to onset of symptom relief in patients with acute attacks of HAE. Two other C1INH treatments are available, both plasma-derived C1INH; one approved for acute HAE, the other approved for long-term prophylaxis. In addition, two other treatments are available for acute HAE (ecallantide, icatibant). There are no direct comparison trials, and the different methods and instruments used to evaluate treatment response make it difficult to guide therapy selection. Selection of treatment should take into consideration the patient's frequency and severity of attacks and previous response to therapy, access to emergency care facilities or ability to self-administer the medication, side effects, quality of life, and cost.

Background

Purpose for review	Recent FDA approval. Issues to be determined: ✔ Does the evidence show that rhC1INH is effective for the treatment of acute HAE attacks? ✔ Are there other beneficial effects of rhC1INH? ✔ Does rhC1INH offer advantages to currently available alternatives? ✔ What safety issues need to be considered with the use of rhC1INH? ✔ Does rhC1INH have specific characteristics best managed by the non-formulary process or criteria for use?
Other therapeutic options[6-10]	The following medications have been FDA approved for the management of acute attacks of HAE and are available non-formulary.

Select Non-Formulary Alternatives	Comments
pdC1INH (human) (BERINERT)	The pdC1INH BERINERT is approved for treatment of acute abdominal or facial attacks of HAE in adult and adolescent patients. Another pdC1INH CINRYZE was approved for routine prophylaxis against angioedema attacks in adolescent and adult patients with HAE, and has also been evaluated for the treatment of acute HAE attacks.
Ecallantide (KALBITOR)	Ecallantide is a plasma kallikrein inhibitor approved for the treatment of acute attacks of HAE.
Icatibant (FIRAZYR)	Icatibant is a bradykinin B2 receptor antagonist approved for the treatment of acute attacks of HAE.

Efficacy (FDA Approved Indications)[1,3-5]

Literature Search Summary
A literature search was performed on PubMed/Medline (1970 to April 2015) using the search term C1 esterase inhibitor, conestat alfa, or RUCONEST. The search was limited to clinical trials performed in humans and published in the English language. Reference lists of review articles were searched for relevant clinical trials. Randomized controlled Phase 3 trials published in peer-reviewed journals evaluating the FDA approved indication were included.

Review of Efficacy[1,3-5]

- FDA labeling for C1 esterase inhibitor (RUCONEST) in patients with an acute HAE attack was based on: one published Phase 3, randomized, placebo-controlled trial (Study 1310) with efficacy evaluated based on patient responses on a Treatment Effect Questionnaire (TEQ),[3] including an open-label extension phase; data from a North American placebo-controlled study (dose of rhC1INH 50 IU/kg or 100 IU/kg) and a European placebo-controlled study (dose of rhC1INH 100 IU/kg), both using a visual analog scale (VAS) to assess treatment response;[1] as well as data from two additional open-label extension trials.[1,4,5]
- The published trials were funded by: Pharming Technologies, B.V.; Santarius, Inc.
- In Study 1310, patients presenting with an acute HAE attack and treated with rhC1INH experienced a reduction in the primary efficacy endpoint of time to onset of sustained relief that was statistically significant compared to placebo. The secondary endpoint of time to minimal symptoms was also shorter with rhC1INH, but was not significantly different compared to placebo.[3] The open-label extension phase of this trial reported similar response with treatment of rhC1INH for repeated attacks.[1]
- Overall, there is low quality of evidence for the use of rhC1INH for the reduction in time to response of an acute HAE attack compared to placebo (Refer to Appendix A).

Study 1310[3]

- Study 1310 was a Phase 3, multicenter, multinational (U.S., South Africa, Italy, Israel, Romania, Poland, Hungary, Bulgaria, Macedonia, and Serbia), double-blind trial that randomized 75 patients with HAE (based on clinical symptoms and baseline plasma C1INH activity < 50% of normal) to rhC1INH (50 IU/kg if < 84 kg; 4200 IU if ≥ 84 kg) or placebo (saline) for treatment of an eligible HAE attack (defined as: peripheral, abdominal, facial, and/or oropharyngeal-laryngeal location; onset occurring within 5 hours of presentation for treatment; Overall Severity VAS score ≥ 50 mm upon presentation and before treatment; and without a decrease in symptoms of ≥ 20 mm Overall Severity VAS score between presentation and treatment). Rescue medication with rhC1INH was permitted at 4 hours or earlier if the patient experienced life-threatening oropharyngeal-laryngeal symptoms of angioedema; other rescue medications (ecallantide, icatibant, pdC1INH) were permitted at any time per provider discretion. Response was evaluated using the TEQ, VAS, and Investigator Score (IS; severity of patient symptoms on scale of 0 to 5). The TEQ was used as the primary efficacy assessment for the endpoint of time to onset of sustained relief (defined as response of "a little better", "better", or "much better" to Question 1 of extent of Overall Severity of HAE attack since treatment; response of "yes" to Question 2 that their symptoms had begun to noticeably decrease; and persistence of improvement as per the same or better response to Question 1, and "yes" to Question 2). A secondary efficacy endpoint using the TEQ was the time to minimal symptoms (Question 3). Patients were assessed using the TEQ, VAS and IS at 15 minute intervals for the first 2 hours, then every 30 minutes through 6 hours; at which time the patient was discharged home and instructed to complete the TEQ and VAS at the 8, 12, and 24 hour time points. Those who did not demonstrate the beginning of persistent relief of symptoms at the 24 hour assessment period were censored at the last assessment time point.
- Approximately 96% of patients were Caucasian, 63% female, and were a mean age of approximately 40 years (range 17 to 69). Prior to enrollment, the mean number of HAE attacks per year were 24.9 (range 0 to 143) in the rhC1INH treatment group and 30.6 (range 3 to 111) in the placebo group. The baseline Overall Severity based on VAS (100 mm scale) was similar between the two groups (rhC1INH 73.5; placebo 77.3). Approximately 50% of patients were being treated with prophylactic maintenance therapy. The primary attack locations for the rhC1INH and placebo groups, respectively, were as follows: peripheral 44% vs. 45%; abdominal 37% vs. 39%; facial 14% vs. 6%; oropharyngeal-laryngeal 5% vs. 10%.

- The primary efficacy endpoint (per TEQ) of time to onset of sustained relief (at primary attack location) was significantly shorter in patients treated with rhC1INH compared to placebo (90 minutes vs. 152 minutes; P=0.031). Sensitivity analyses were conducted to account for use of rescue medications, or a more robust response (i.e., based on "better" or "much better", excluding "a little better"), which also showed a significant decrease in the primary endpoint. When time to onset of sustained relief was assessed by VAS (decrease in score of $\geq$ 20 mm) or IS (decrease of $\geq$ 1), the results were also significantly shorter with rhC1INH compared to placebo. The secondary endpoint of time to minimal symptoms (per TEQ) was shorter with rhC1INH, but was not significantly different compared to placebo. Details of these results are provided in the table below.

Study 1310 Results[3]

Endpoint (minutes)	rhC1INH (N=44)	Placebo (N=31)	P
	Median (95% Confidence Interval)		
Primary[a] TEQ	90 (61 to 150)	152 (93 to -)	0.031
VAS[b]	75 (60 to 105)	303 (81 to 720)	0.003
IS[c]	60 (49 to 75)	105 (75 to -)	<0.001
Sensitivity analyses			
Use of rescue medications[d]	90 (61 to 150)	334 (105 to 1,440)	0.010
Modified response[e]	122 (90 to 180)	304 (150 to -)	0.001
Secondary[f] TEQ	303 (240 to 720)	483 (300 to 1,440)	0.078

[a] Time to onset of sustained relief per Treatment Effect Questionnaire (TEQ)
[b] Time to onset of sustained relief per Visual Analog Scale (VAS)
[c] Time to onset of sustained relief per Investigator Score (IS)
[d] Time to onset of relief set at 24 hours in patients who received rescue or disallowed concomitant medication
[e] Onset of relief based on "better" or "much better"
[f] Time to minimal symptoms at all attack locations

- Of the patients who responded within 4 hours, 1 patient in the rhC1INH group and 4 patients in the placebo group experienced a relapse of their symptoms within 24 hours.[1,3] In addition, 4 patients treated with rhC1INH and 11 patients in the placebo group were treated with rescue medication with rhC1INH.[3]
- Per the manufacturer's product information, results of a planned subgroup analyses reported the primary efficacy endpoint in the U.S. sites to be 98 minutes (95% CI 45 to 240; N=22) in patients treated with rhC1INH vs. 90 minutes (95% CI 50 to - ; N=16) with placebo; and 90 minutes (95% CI 63 to 120; N=22) with rhC1INH vs. 334 minutes (95% CI 150 to - ; N=15) with placebo, in non-U.S. patients. There was also a larger treatment effect in the subgroup of men compared to the response in women. The product information states a potential explanation for the regional difference in response may be due to the large placebo response in U.S. women.[1]
- The 44 patients who received treatment with rhC1INH in Study 1301 were followed and treated for a total of 170 attacks during the open-label extension period. The median time to onset of symptom relief was reported as 75 minutes (95% CI 64 to 90). Of the 170 attacks, 5 (3%) received a second dose of rhC1INH.[1]

North American Trial and European Trial[1,4,5]

- Additional support for the FDA approval of rhC1INH in acute attacks of HAE comes from results of the North American trial (rhC1INH: 50 IU/kg N=12, 100 IU/kg N=13; placebo N=13) and European trial (rhC1INH 100 IU/kg N=16; placebo N=16) as reported in the manufacturer's product information.[1] Time to onset of relief as indicated by a $\geq$ 20 mm decrease on the patient's VAS from baseline, with persistence at 2 consecutive evaluations, was significantly reduced with rhC1INH compared to placebo (specific data points not reported).[1]
- In the North American open-label extension trial (March 2007 to January 20, 2010), 62 patients were treated for 168 attacks, with 90% of attacks treated with a single dose of rhC1INH 50 IU/kg, and greater than 90% of attacks responded (based on a decrease of $\geq$ 20 mm VAS) within 4 hours after treatment. For the first 5 attacks, the median time to onset of symptom relief was 37 to 67 minutes, with median time to minimal symptoms 120 to 244 minutes. The breakdown for number of attacks treated was as follows: 20 patients treated for 1 attack; 34 patients treated for 2 to 5 attacks; and 8 patients treated for 6 to 8 attacks. It was reported that there was no additional dose increase seen with subsequent attacks. There were 23 (37%) patients receiving maintenance or prophylactic therapy. There were 20 serious adverse events reported, with none considered to be related to study treatment. Two patients had anti-rhC1INH antibody results at a single time point, as well as isolated, transient anti-HRI (host-related impurities) antibodies. These patients did not report treatment-related adverse events, and there was no reported effect on treatment efficacy. There were no neutralizing anti-rhC1INH antibodies observed in any of the patients.[4]

- In the European open-label extension trial, 57 patients were treated for 194 attacks, using a fixed-dose of rhC1INH 2100 IU (one vial; with up to 2 additional vials at the discretion of the investigator). Treatment doses were 2100 IU in 110 (57%), 4200 IU in 68 (35%), and 6300 IU in 15 (8%) of patients. Sustained relief (based on a decrease of $\geq$ 20 mm VAS) was maintained at 4 hours in 87% of attacks. The median time to onset of symptom relief for attacks 1 through 5 was 60 to 120 minutes. The breakdown for number of attacks treated was as follows: 16 patients treated for 1 attack; 34 patients treated for 2 to 5 attacks; 7 patients treated for $\geq$ 6 attacks. The number of vials used did not increase with the number of attacks. There were 31 (54.4%) patients receiving maintenance or prophylactic therapy. No serious adverse events were reported within 7 days of dose administration, and there were no deaths or discontinuations due to adverse events. There was no noted relationship between the presence of anti-rhC1INH antibodies and response to treatment or adverse events. There were no neutralizing anti-rhC1INH antibodies observed in any of the patients.[5]

Potential Off-Label Use[11]

- rhC1INH is approved for the treatment of acute attacks of HAE, and is recommended to be initiated under the supervision of a qualified healthcare professional who is experienced in the treatment of HAE. According to the manufacturer's product information, patients who have received appropriate training may self-administer rhC1INH upon recognition of an HAE attack (i.e., on-demand therapy).[1] In addition to treatment of acute attacks, rhC1INH is also being studied for use as prophylaxis of HAE attacks. According to a pilot study of 25 patients with HAE who reported a mean of 0.9 HAE attacks per week over the previous 2 years, when treated with rhC1INH 500 IU once weekly as prophylaxis, breakthrough attacks were reported at a mean of 0.4 per week.[11]
- Although not with the rhC1INH (RUCONEST), there is an ongoing clinical trial with the pdC1INH (BERINERT) in the treatment of patients with angiotensin-converting enzyme inhibitor (ACEI)-induced angioedema (refer to www.clinicaltrials.gov).

Safety[1]
(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	- None
Contraindications[1]	- Known or suspected allergy to rabbits and rabbit-derived products. - History of immediate hypersensitivity reactions, including anaphylaxis, to C1 esterase inhibitor preparations.
Warnings/Precautions[1]	- **Hypersensitivity reactions**, including anaphylaxis may occur; if symptoms occur, discontinue rhC1INH and administer appropriate treatment. - **Serious arterial and venous thromboembolic events** have been reported at the recommended dose of plasma derived C1 esterase inhibitors in patients with risk factors. It is recommended to monitor patients with known risk factors for thromboembolic events during and after rhC1INH administration.

Safety Considerations[1]
- The manufacturer's product information states that the serious adverse reaction reported in clinical trials with rhC1INH is anaphylaxis.
- As rhC1INH is a therapeutic protein, there is potential for immunogenicity. Testing for pdC1INH or rhC1INH antibodies as well as for antibodies against host-related impurities (HRI) was performed in 205 patients treated with rhC1INH with the following results: anti-C1INH antibodies were detected in 0.6% to1.0% of samples tested after first exposure, and in 0.5 to 2.2% of samples tested after repeated exposure; anti-HRI antibodies was in 3.5% to 4.6% of samples tested after first exposure, and 5.7% to 17% of samples after repeated exposure; $\geq$ 10% of patients had an antibody response to rhC1INH after five treated HAE attacks; no anti-C1INH neutralizing antibodies were detected and anti-C1INH and anti-HRI antibodies were not associated with adverse clinical findings. It is noted that it is difficult to compare the incidence of antibodies to rhC1INH compared to other products due variables including sensitivity and specificity of the assay, assay methodology, handling of the sample and timing of sample collection, concomitant medications, and underlying disease.

Adverse Reactions[1,3-5]

Common adverse reactions[1]	Headache (9%), nausea (2%), diarrhea (2%), were reported in $\geq$ 2% patients in clinical trials with rhC1INH.
Death/Serious adverse reactions[1,3-5]	There were no deaths reported in one phase 3, randomized, placebo-controlled trial or in two open-label extension studies.[1,3-5] Most of the reported treatment emergency adverse events were of mild or moderate severity, with 3 patients experiencing a severe treatment emergency adverse event (rhC1INH: urinary tract infection, abdominal hernia; placebo: sinus congestion) that were not considered to be related to the study drug.[3]
Discontinuations due to adverse reactions[3]	There were no discontinuations due to treatment emergency adverse events reported in one clinical trial (noting this study was for treatment of an acute attack, allowing for rescue therapy at 4 hours).

Drug Interactions[1]

Drug-Drug Interactions[1]
- None reported.

Risk Evaluation

As of April 2, 2015

	Comments
Sentinel event advisories	- None
Look-alike/sound-alike error potentials	(see table below)

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
C1 esterase inhibitor (recombinant)	None	None	None	C1 esterase inhibitor (human) Cinestin
RUCONEST	None	None	None	Rhinocort (look-alike name) Scandonest Levonest

- Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Other Considerations[1,6,7]

- There are three available C1INH (refer to Appendix), that differ in their FDA approved indications.[1,6,7] It is noted that all three C1INH products provide instructions for self-administration.[1,6,7] No direct comparison trials are available to determine if there is a difference in efficacy or safety.
- Two of the C1INH products are derived from human plasma, and therefore have the potential for human viral transmission. Both pdC1INH products (BERINERT; CINRYZE) undergo several steps in the manufacturing process to reduce the risk of viral transmission.[6,7] According to the manufacturers, neither product has been confirmed to be associated with a viral transmission.[6,7] rhC1INH is purified from the milk of transgenic rabbits to reduce the risk for human viral transmission.[1]

Dosing and Administration[1]

- rhC1INH (RUCONEST) is for intravenous use after reconstitution only.
- The recommended dose of rhC1INH is 50 IU per kg with a maximum of 4200 IU to be administered as a slow intravenous injection over approximately 5 minutes. If symptoms of the attack persist, a second dose can be administered at the recommended dose level (not to exceed 4200 IU per dose). It is recommended that no more than 2 doses be administered within a 24 hour period.

- It is recommended that rhC1INH treatment be initiated under the supervision of a qualified healthcare professional who is experienced in the treatment of HAE. Patients who have received appropriate training may self-administer rhC1INH upon recognition of an HAE attack.
- Refer to the manufacturer's product information for Preparation and Handling, Reconstitution, and Administration.

Special Populations (Adults)[1]

	Comments
Elderly[1]	• Clinical studies with rhC1INH included an insufficient number of patients over the age of 65 (i.e., 7 patients) to determine if older patients respond differently from younger patients.
Pregnancy[1]	• rhC1INH is Pregnancy Category B • There are no adequate and well-controlled trials in pregnant women. • The manufacturer's product information states that studies performed in rats and rabbits at doses up to 12.5 times the human dose of 50 IU/kg could not exclude an effect on embryofetal development; because animal reproduction studies are not always predictive of human response, rhC1INH should only be used during pregnancy if clearly needed. • The safety and efficacy of rhC1INH given prior to or during labor and delivery have not been established; use only if clearly needed.
Lactation[1]	• It is not known if rhC1INH is excreted in human milk. As many drugs are excreted in human milk, caution is advised when rhC1INH is administered to a nursing woman.
Renal Impairment	• No data identified.
Hepatic Impairment	• No data identified.
Pharmacogenetics/genomics	• No data identified.

Projected Place in Therapy

- Hereditary angioedema is an autosomal dominant disorder caused by a deficiency in functional C1 inhibitor and has been estimated to affect approximately 1 in 50,000 persons (there are estimated to be approximately 6,000 patients in the United States with HAE). Hereditary angioedema would be expected to be uncommon in the VA since patients usually first present with symptoms in early childhood.[2,10]
- Patients often experience attacks of HAE for the duration of their lives. The frequency of attacks is variable, occurring on average every 1 to 2 weeks. Some patients will rarely experience an attack while others have them on a more frequent basis.[2,10] The most common location for an acute attack is the skin or abdomen, with attacks of the skin most commonly involving the extremities, then face, genitals, and chest/neck. Symptoms may include swelling (most common in the hands, feet, arms, legs, and abdomen; less frequently involving the oropharynx) and a nonpruritic rash; often associated with tingling prior to the appearance of symptoms. Swelling may worsen over the first 24 hours then diminish over the next 2 to 3 days. Symptoms associated with the abdomen also include pain, nausea, vomiting, and hypotension due to a shift in fluid. Death has occurred with laryngeal angioedema. Triggers may include stress or trauma, including surgical or dental procedures; although, attacks may occur without a precipitating factor.[2]
- Diagnosis can be made in a patient with a history of recurrent angioedema, and abdominal pain without urticaria. Measurement of C4 levels can be used to rule-out HAE, since nearly all patients with HAE will have decreased levels. Further testing may be conducted to evaluate the antigenic or functional C1 inhibitor level to determine the HAE type.[2,12] Patients with HAE have a mutation in the C1 inhibitor gene and may be classified as type I (85% of patients) or type II (15%), the two main types of HAE that result in reduced levels of antigenic (type I) and functional (type I and II) levels of C1 inhibitor. Another type of familial angioedema has been described, primarily involving women during pregnancy or who received estrogen therapy (although, this form has also been found in men), that present with normal levels of antigenic and functional C1 inhibitor.[2]
- Recombinant human C1INH (RUCONEST) appears to be effective in reducing the time to onset of symptom relief in patients with acute attacks of HAE, although a significant difference in response was not seen in a

subgroup of U.S. patients, potentially due to the placebo response seen in women.[1,3-5] Two other C1INH treatments are available, both plasma-derived C1INH; one FDA approved for acute HAE (BERINERT), the other approved for long-term prophylaxis (CINRYZE).[6,7] The rhC1INH (RUCONEST) is thought to offer an advantage over pdC1INH to decrease the risk for human viral transmission, although neither of the pdC1INH products has been confirmed to be associated with viral transmission.[6,7] In addition, two other treatments are available for acute HAE (ecallantide, icatibant). There are no direct comparison trials, and the different methods and instruments used to evaluate treatment response make it difficult to compare treatment results or guide therapy selection.

- Management of HAE includes recognition and avoidance of potential triggers, treatment of acute symptoms, and short and long-term prophylaxis.[2,12-15] For the management of significant acute HAE attacks, use of a C1INH, ecallantide, or icatibant are considered treatment options.[2,12-15] Fresh frozen plasma that contains C1 inhibitor has also been used for acute attacks although it is controversial as to whether treatment can exacerbate symptoms in some patients due to the potential for bradykinin production.[2,10,12,16] Symptom control of acute attacks includes narcotic analgesics for abdominal pain, antiemetics, and hydration. Intubation may be necessary in patients with oropharyngeal involvement if closure of the airway occurs.[2] The attenuated androgens (e.g., danazol, oxandrolone, stanozolol) and antifibrinolytics (e.g., aminocaproic acid, tranexamic acid) are more often used for long-term or short-term prophylaxis of HAE; although, they have been used in the management of acute HAE attacks,[2,12,14,15] despite not being adequately studied or to have confirmed benefit in this setting. The use of C1INH has also been studied and recommended as an option in short-term or long-term prophylaxis,[2,7,10,12-15] with CINRYZE being the only C1INH currently approved for routine prophylaxis.[7] Determination of whether the patient would benefit from on-demand therapy (e.g., self-administration by the patient at the onset of an acute attack) or long-term prophylaxis should take into consideration patient factors such as age, comorbidities, and access to emergency care facilities, as well as the patient's frequency and severity of attacks and previous response to therapy.[12] The safety and efficacy of treatment with a C1INH in the management of ACEI-induced angioedema has not been established.

- Overall, there is low quality of evidence for the use of rhC1INH for the reduction in time to response of an acute HAE attack compared to placebo (Refer to Appendix A).

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Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.

Appendix: Product Comparison (refer to individual VA National Drug Monographs www.pbm.va.gov)

	C1 Inhibitor (RUCONEST)	Icatibant (FIRAZYR)	Ecallantide (KALBITOR)	C1 Inhibitor (BERINERT)	C1 Inhibitor (CINRYZE)
FDA indication	Acute attacks HAE	Acute attacks HAE	Acute attacks HAE	Acute abdominal, facial or laryngeal attacks of HAE	Routine prophylaxis against HAE attacks
Published data in HAE	Acute HAE (RCT) Long-term prophylaxis HAE (pilot study) On-demand therapy HAE (prospective case study)	Acute HAE (RCT) Short-term prophylaxis HAE (Case report) On-demand therapy HAE (Observational study/OL study/Case report)	Acute HAE (RCT)	Acute HAE (RCT) Long-term prophylaxis HAE (Registry data; OL trial with preliminary results [unpublished]) Short-term prophylaxis HAE (Retrospective analysis/prospective survey) On-demand therapy HAE (Registry data) Per PI: Safety and efficacy for prophylactic therapy have not been established	Acute HAE (RCT) Long-term prophylaxis HAE (RCT) Short-term prophylaxis HAE (Case report) On-demand therapy HAE (Observational)
HAE attack location studied	Abdominal, facial, peripheral or oropharyngeal- laryngeal HAE Limitation of Use (per PI): Effectiveness was not established in HAE patients with laryngeal attacks	Abdominal, cutaneous HAE; laryngeal HAE	HAE attack of any location	Abdominal, facial HAE; open-label extension: abdominal, facial, peripheral or laryngeal HAE	HAE attack of any location
Inclusion RCT (Acute HAE)	Report w/in 5 hours acute peripheral, abdominal, facial, and/or oropharyngeal-laryngeal HAE with Overall Severity VAS score $\geq$ 50 mm (and without decrease in sx of $\geq$ 20 mm Overall Severity VAS score between presentation and tx)	Report w/in 6 hours acute HAE becoming moderately-severe (Study 1 &2: abdominal, cutaneous; Study 3: abdominal, cutaneous; laryngeal OL tx)	Report w/in 8 hours acute HAE becoming moderate-severe	Report w/in 5 hours acute facial or abdominal HAE becoming moderate in intensity	Report w/in 4 hours acute HAE (off-label tx); moderate-severe abdominal, facial, genital (most severe=defining site); laryngeal
Primary Endpoint	Median time to onset sustained relief (per TEQ "a little better", "better", or "much better" to change in Overall Severity of HAE attack since tx (Q1); response of "yes" if sx had begun to noticeably decrease (Q2); and persistence of improvement as per the same or better response to Q1, and "yes" to Q2)	(Study 1& 2) Median time to clinically significant relief (1st of 3 measures $\geq$ 20 to 30 mm reduction in VAS of 0 to 100 mm) of index sx (Study 3) Median time to onset relief (50% reduction sx severity) composite sx	(Study 1) Tx outcome score (+100 significant improvement to -100 significant worsening) at 4 hrs (Study 2) Change sx score (0 normal to 3 severe) at 4 hrs	Median time to onset relief (1st of 3 reports of relief or resolution at defining site) assessed per questions at intervals for up to 24 hrs	Acute: Median time to onset relief (1st of 3 reports of improvement at defining site) assessment per standard questionnaire every 15 min up to 4 hrs Prophylaxis: Number attacks per 12 wk tx period
Treatment Comparison	C1 INH 50 units/kg IV vs. placebo	(Study 1 & 3) Icatibant 30 mg SC vs. placebo (Study 2) Icatibant 30 mg SC vs. tranexamic acid 3 gm daily X 2 days	Ecallantide 30 mg SC vs. placebo	C1 INH 10 or 20 units/kg IV vs. placebo	Acute: C1 INH 1000 units IV vs. placebo Prophylaxis: C1 INH 1000 units IV 2 x/wk vs. placebo

Continued	rhC1 Inhibitor (RUCONEST)	Icatibant (FIRAZYR)	Ecallantide (KALBITOR)	pdC1 Inhibitor (BERINERT)	pdC1 Inhibitor (CINRYZE)
Results	PEP (Acute): 90 min (1.5 hrs) vs. 152 min (2.53 hrs); (P=0.031) Median time to minimal sx: 303 min (5.05 hrs) vs. 483 min (8.05 hrs) (P=0.078	PEP (Study 1): 2.5 hrs vs. 4.6 hrs (P=0.14) Median time to almost complete sx relief: 8.5 hrs vs. 19.4 hrs (P=0.08) PEP (Study 2): 2.0 hrs vs. 12.0 hrs (P<0.001) Median time to almost complete sx relief: 10.0 hrs vs. 51.0 hrs (P<0.001) PEP (Study 3): 2.0 hrs vs. 19.8 hrs (P<0.001) Median time to almost complete sx relief: 8.0 hrs vs. 36.0 hrs (P<0.001)	PEP (Study 1): Median 50 vs. 0 (P=0.004) Median time to onset overall sx improvement: 2.75 hrs vs. > 4 hrs (P=0.14) PEP (Study 2): Median -1 vs. 0 (P=0.01)	PEP (Acute): 0.5 hrs (20 units/kg) vs. 1.5 hrs (P=0.0025) Median time to complete resolution: 4.92 hrs vs. 7.79 hrs (P=0.0237)	PEP (Acute): 2 hrs vs. > 4 hrs (P=0.02) Median time to complete resolution: 12.3 hrs vs. 25 hrs (P=0.004) Prophylaxis: 6.26 vs. 12.73 attacks (P<0.001)
Warnings and Precautions	Hypersensitivity Thrombotic events (reported with pdC1INH in patients with risk factors)	Seek immediate medical attention if acute laryngeal HAE attack	Boxed warning for anaphylaxis	Hypersensitivity Risk for transmission of infectious agents Thrombotic events	Hypersensitivity Risk for transmission of infectious agents Thrombotic events
Product Description	Recombinant analogue of human C1INH purified from the milk of transgenic rabbits	Synthetic decapeptide with 5 non-proteinogenic amino acids	Amino acid protein produced in *Pichia pastoris* yeast cells by recombinant DNA technology	Derived from human plasma (pasteurized, nanofiltered)	Derived from human plasma (pasteurized, nanofiltered)
Product availability	Available as a lyophilized powder for reconstitution for injection in a single-use 25 ml vial; each vial contains 2100 IU of rhC1INH.	One ready-to-use pre-filled syringe of 30 mg/3 mL required to deliver 30 mg administered SC	Package containing 3 single-use vials each with 10 mg/mL (1 mL), with 3 separate SC injections required to administer dose of 30 mg	Kit containing 500 units powder in single-use vial for reconstitution with 10 mL sterile water and Mix2Vial transfer set; required number of vials are reconstituted to obtain dose of 20 units per kg combined in syringe, with use of IV administration set to deliver dose at rate of 4 mL/min	Available as 500 units powder for reconstitution with 5 mL sterile water using double-ended transfer needle for concentration 100 units/mL; combining 2 vials in syringe, with use of appropriate needle/IV administration set for delivery of 1000 units dose at rate of 1 mL/min over 10 min
Dose	< 84 kg: 50 units per kg ≥ 84 kg: 4200 units	30 mg	30 mg	20 units per kg	1000 units
Route of administration	Slow IV infusion over 5 min Instructions and training available for self-administration	SC injection (one 3 mL injection) Instructions and training available for self-administration	SC injection (3 injections per dose) Recommendations to only be administered by healthcare professional with medical support available to manage anaphylaxis and HAE	IV infusion (4 mL/min) (duration of infusion depends on dose based on weight) Approved for on-demand self-administration; instructions and training available	IV infusion (1mL/min) (10 min per dose) Instructions and training available for self-administration
Storage	Below or at 77° F Protect from light	36° to 77° F Store in container until ready to use	Refrigerate (36° to 46° F) Protect from light	36° to 77° F Protect from light	36° to 77° F Protect from light
Shelf-life	Up to 4 years	Up to 24 months	Up to 36 months	Up to 30 months	Up to 24 months
Special Handling	Available for purchase from ASD Healthcare and Cardinal; no specialty pharmacy requirements	Available for purchase from McKesson; no specialty pharmacy requirements	Available for purchase from ASD Healthcare; no specialty pharmacy requirements	Available for purchase from McKesson Plasma & Biologics; dispensed from local VA pharmacy	Available for purchase from Curascript; can be dispensed by local VA pharmacy or specialty pharmacy

C1 INH=C1 inhibitor; HAE=hereditary angioedema; hrs=hours; IV=intravenous; min=minute; OL=open-label; PI=product information; pd=plasma-derived; RCT=randomized controlled trial; rh=recombinant human; SC=subcutaneous; sx=symptom; TEQ=Treatment Effect Questionnaire; tx=treatment; VAS=visual-analogue scale